Delayed Therapy with Plasma Gelsolin Improves Survival in Murine Pneumococcal Pneumonia

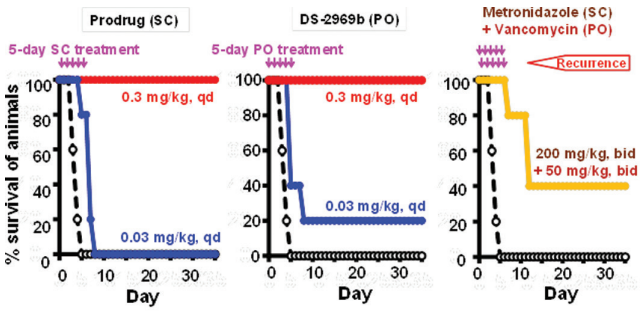

Fig. 1 Efficacy in hamster CDI model caused by *C. difficile* 2009155 (NAP1/027)

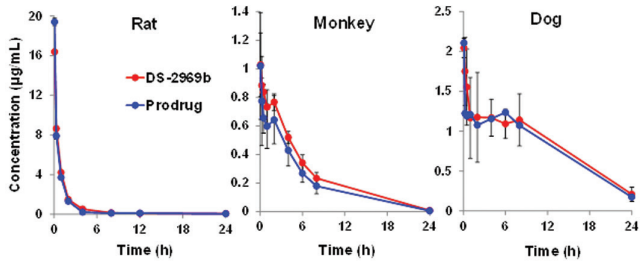

Fig. 2 Plasma concentrations of DS-2969a after IV administration of DS-2969b and its prodrug at 12.5 (rat) and 1 (monkey, dog) mg/kg as DS-2969a

Disclosures. **M. Yamada**, Daiichi Sankyo Co., Ltd.: Employee, Salary; **M. Uchiyama**, Daiichi Sankyo Co., Ltd.: Employee, Salary; **S. I. Inoue**, Daiichi Sankyo Co., Ltd.: Employee, Salary; **T. Deguchi**, Daiichi Sankyo Co., Ltd.: Employee, Salary; **Y. Furuta**, Daiichi Sankyo Co., Ltd.: Employee, Salary; **K. Yabe**, Daiichi Sankyo Co., Ltd.: Employee, Salary; **N. Masuda**, Daiichi Sankyo Co., Ltd.: Employee, Salary

1517. ZTI-01 Treatment Improves Survival of Animals Infected with Multidrug Resistant *Pseudomonas aeruginosa*

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Background. ZTI-01 (fosfomycin, FOS, for injection) is currently under US development to treat complicated urinary tract infections. ZTI-01 is unique compared with other antimicrobials in that it inhibits an early step in cell wall synthesis via covalent binding to MurA. ZTI-01 demonstrates broad *in vitro* activity against Gram-negative (GN) and -positive (GP) bacteria, including multidrug-resistant (MDR) organisms. Our study goals were to determine the efficacy of ZTI-01 as a monotherapy or in combination with meropenem against MDR *Pseudomonas aeruginosa* in a preclinical model of pulmonary infection.

Methods. 8 week old neutropenic mice were infected with a MDR strain of *P. aeruginosa* via intubation-mediated intratracheal (IMIT) instillation. 3 hours after instillation, mice received treatment with ZTI-01, meropenem, or ZTI-01 plus meropenem (combination therapy) q8h for 5 days. Mice were monitored every 8 hours for 7 days for development of disease and moribund animals were humanely euthanized. Lungs and spleens were harvested at euthanasia, or at 7 days for survivors, and processed for bacterial enumeration and development of pathology.

Results. Mice were challenged with a lethal dose of *P. aeruginosa* UNC-D. Mock treated animals succumbed to infection within 36 hours post-infection. Animals that received 6 g/kg/day ZTI-01 showed an increase in the MTD (52 hours) and 25% of the cohort were protected from lethal disease. Combining ZTI-01 with meropenem resulted in a significant increase in survival (≥75% of cohorts survived infection). Combination therapy also significantly decreased bacterial numbers in the lungs and inhibited dissemination to the spleens. Furthermore, animals receiving combination therapy were protected from significant inflammation in the lungs and the development of pneumonia.

Conclusion. Here we report that combination therapy with ZTI-01 and meropenem provides significant improvements in all disease manifestations over treatment with each drug individually in a preclinical model for pulmonary infection with MDR *P. aeruginosa*. These data strongly support further evaluation of ZTI-01 in combination with other antibiotics as potential therapies against pulmonary infections with MDR bacteria.

Disclosures. **E. J. Ellis-Grosse**, Zavante Therapeutics, Inc.: Employee and Shareholder, Salary

1518. Evaluation of the Efficacy of CD101, a Novel Echinocandin, in the Treatment of *Candida auris* Infection Using a Murine Model of Disseminated Candidiasis

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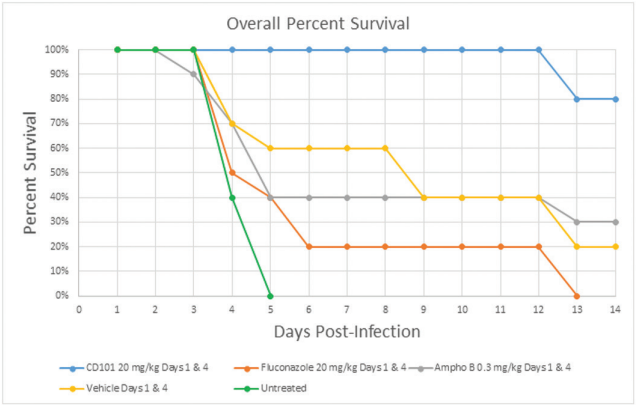
Background. The first case of an invasive infection caused by *C. auris* was reported in July of 2016. Multiple cases have since been reported with high mortality rates due to the multidrug-resistant nature of *C. auris*. Although *C. auris* shows increased susceptibility to the echinocandin class of antifungals, the use of these drugs is restricted to multiple IV administrations. CD101 is a novel echinocandin with enhanced stability and pharmacokinetics, allowing for once weekly high dose administration. In this study, we evaluated the efficacy of CD101 in the treatment of disseminated *C. auris* infection using a murine model of disseminated candidiasis.

Methods. Female 6–8 week old CD-1 mice were immunosuppressed with cyclophosphamide (200 mg/kg) 3 days prior to infection and 150 mg/kg 1 day post-infection. On the day of infection, mice were inoculated with 3 x 10^7 *C. auris* blastospores via the lateral tail vein. Mice were randomized into 5 groups ($n = 5$ for colony forming units (CFU) and $n = 10$ for survival): CD101 20 mg/kg administered by intraperitoneal (IP) injection, fluconazole 20 mg/kg administered per os (PO), amphotericin B 0.3 mg/kg IP, and a vehicle control. Treatments were administered 2 hours post-infection (day 1) and again on day 4 of the study for a total of 2 doses. Mice were monitored daily and a survival curve was generated. CFU groups were sacrificed on day 8 of the study. One kidney was removed from each mouse, homogenized, plated on potato dextrose agar (PDA), and incubated at 35°C for 2 days to determine CFU. The remaining survival mice were monitored until the end of the study (day 14).

Results. CD101 showed an average 3 log reduction in kidney CFU compared with fluconazole, amphotericin B, and vehicle treated groups, which was statistically significant ($P = 0.03$, 0.03, and 0.04, respectively). At the end of the study, percent survival of mice in CD101, fluconazole, amphotericin B, vehicle, and untreated groups was 80, 0, 30, 20, and 0%, respectively (Figure 1).

Conclusion. Taken together, our findings show that CD101 possesses potent antifungal activity against *C. auris* infection in a disseminated model of candidiasis. Additionally, treatment with CD101 resulted in a significantly higher overall percent survival. Further investigation of this drug is warranted.

Figure 1. Survival curve of mice in all treatment groups after 14 days.



Disclosures. **M. Ghannoum**, Amplyx Pharmaceuticals: Consultant, Research Contractor and Scientific Advisor, Consulting fee and Research grant; Cidara Therapeutics: Consultant and Research Contractor, Consulting fee and Research grant

1519. Delayed Therapy with Plasma Gelsolin Improves Survival in Murine Pneumococcal Pneumonia

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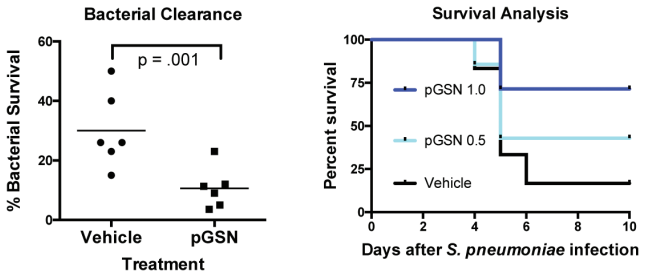
Background. Innate immune responses contribute to successful resolution of bacterial pneumonia. Bolstering host defense with immunomodulators might be increasingly needed to improve outcomes in antibiotic-resistant infections. One

candidate molecule is recombinant human plasma gelsolin (rhu-pGSN), an abundant normal blood protein whose levels fall proportionally with disease severity. Pretreatment with rhu-pGSN has beneficial effects in many pre-clinical models of inflammation and injury, including pneumonia. We evaluated the effects of delaying therapy with rhu-pGSN up to 48 hours after lethal intra-nasal pneumococcal challenge in a mouse model to more closely mimic realistic clinical circumstances.

Methods. Adult Bl/6 mice were inoculated intra-nasally with *S. pneumoniae* serotype 3 on day 0, followed by subcutaneous rhu-pGSN 24 hours later for evaluation of bacterial clearance in lavage fluids. To assess effects on survival, rhu-pGSN was administered on days 2 and 3 after infection and effects monitored for 10 days. No antibiotics or other interventions were given.



Results. Treatment with rhu-pGSN at 24 hours after infection improved bacterial clearance, seen as reduction of bacterial CFU in bronchoalveolar lavage fluid at 48 hours (% of initial inoculum, vehicle vs.. rhu-pGSN (dose range 0.5–2 mg): 30 ± 13 vs. 11 ± 7, n = 6 trials using inocula ranging 0.3–1.8 x 10^6 CFU, 3 mice/group/trial, P = .001). In 3 separate trials, pGSN (0.5 mg s.c.) reduced weight loss and mortality (% survival, vehicle vs. pGSN: 40 vs. 80, 0 vs. 25, 17 vs. 43; n ≥ 16/group, P =.02). Increasing the dose to 1 mg further improved survival from 17 to 71%.

Conclusion. Rhu-pGSN can substantially improve survival in a murine model of fatal pneumococcal pneumonia, even when administered as single doses on days 2 and 3 after infection without antibiotics. The data support further evaluation of pGSN as adjunctive therapy for serious infections with diverse pathogens and in models of antibiotic-resistant pneumonia.

Disclosures. **Z. Yang**, BioAegis: Shared NIH grant to study plasma gelsolin, we receive plasma gelsolin for our lab studies; **S. Levinson**, BioAegis: BIoAegis shares a grant to investigate plasma gelsolin with HSPH, Employee and Shareholder, Salary; **T. Stossel**, BioAegis: Consultant and Shareholder, portion of royalties from Hospital IP licensed to BioAegis; **M. DiNubile**, BioAegis: Employee and Shareholder, Consulting fee; **L. Kobzik**, BioAegis: Collaborator and We share a NIH grant on pGSN with BioAegis, we receive plasma gelsolin for our lab studies

1520. *In Vivo* Efficacy of Humanized Exposures of Cefiderocol Compared with Cefepime (FEP) and Meropenem (MEM) against Gram-negative Bacteria in a Murine Thigh Model

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Background. Cefiderocol (S-649266) is a novel siderophore cephalosporin under development by Shionogi (Osaka, Japan). Previous studies have demonstrated cefiderocol efficacy against a diverse population of Gram-negative bacteria with MICs ≤ 4 µg/mL. Our aim was to further define the agent's clinical role by comparing the efficacy of humanized regimens of cefiderocol, FEP, and MEM against a subset of these Gram-negative isolates.

Methods. 15 Gram-negative isolates were studied. MICs were determined by broth microdilution in triplicate, using reference CLSI methods. Pharmacokinetic studies were conducted to reproduce the humanized exposures of cefiderocol 2g q8h (3h inf.), FEP 2g q8h (3h inf.), and MEM 2g q8h (3 hours inf.). Antibiotics were started 2h post thigh inoculation (0h) and continued for 24 hours in immunocompromised mice. Efficacy was determined as the change in $\log_{10}$CFU at 24h compared with 0 hour controls.

Results. 8 Enterobacteriaceae, 4 *A. baumannii*, and 3 *P. aeruginosa* isolates were studied. Cefiderocol, FEP, and MEM MICs were in the range of 0.12 to 8 µg/mL, ≤0.03 to >64 µg/mL, and ≤0.06 to >64 µg/mL, respectively. Three of the 15 isolates were susceptible to both meropenem and cefepime. All remaining isolates demonstrated *in vitro* resistance to one or both comparator agents. Cefiderocol was efficacious against all 15 isolates, regardless of FEP or MEM resistance, producing bacterial reductions from 0 hour between 0.89 to 3.04 $\log_{10}$ CFU. Against FEP and MEM susceptible isolates, cefiderocol treatment resulted in bacterial kill of 2.6 ± 0.5 and 2.1 ± 0.9 $\log_{10}$ CFU, respectively, similar to that of FEP (2.6 ± 0.5) and MEM (2.2 ± 0.6). Against MEM and FEP resistant isolates, cefiderocol produced a mean (± SD) bacterial reduction of 1.5 ± 0.4 $\log_{10}$ CFU at 24 hours.

Conclusion. Cefiderocol humanized exposures produced antibacterial efficacy similar to MEM and FEP for susceptible pathogens, while also displaying activity against Enterobacteriaceae, *A. baumannii*, and *P. aeruginosa* with phenotypic resistance to the comparator β-lactams. These studies support the potential clinical utility of cefiderocol against these difficult-to-treat multidrug-resistant pathogens.

Disclosures. **M. Tsuji**, Shionogi & Co.: Employee, Salary; **Y. Yamano**, Shionogi & Co.: Employee, Salary; **R. Echols**, Shionogi & Co.: Employee, Salary; **D. P. Nicolau**, Shionogi & Co.: Research Contractor, Research support

1521. APX001A Protects Immunosuppressed Mice from *Rhizopus delemar* Infection

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Background. Mucormycosis is a life-threatening infection with high mortality that occurs predominantly in immunocompromised patients. APX001A is an antifungal agent that targets Gwt1, an early step in the conserved glycosylphosphotidyl inositol (GPI) post-translational modification pathway of surface proteins in eukaryotic cells. Inhibition of inositol acylation by APX001A results in pleiotropic effects such as inhibition of maturation of GPI-anchored proteins necessary for growth and virulence and results in lethality. APX001A has in vitro activity against Mucorales. Here we assessed the in vivo activity of APX001A against *Rhizopus delemar* (MIC = 0.25 µg/mL).

Methods. ICR mice were immunosuppressed with cyclophosphamide (200 mg/kg) and cortisone acetate (500 mg/kg) on days -2, +3, and +8 relative to intratracheal infection with 2.5 x 10^5 cells of *R. delemar* 99–880. For survival studies, treatment with APX001 (prodrug) at 52, 104, or 156 mg/kg (twice daily, po), was compared with liposomal amphotericin B (LAmB) at 15 mg/kg (once daily, iv). Treatment started on day +1 through day +8 for APX001 and through day +4 for LAmB. Placebo mice received vehicle control. For fungal burden studies, dosing started 8 hours post infection through day +3. Mice were sacrificed on day +4. Survival time, and tissue fungal burden (by qPCR) served as efficacy endpoints.

Results. APX001 treatment at either 52 or 104 mg/kg prolonged survival of mice vs. placebo (n = 20 per arm) (21-day survival of 0% for placebo, 30% for 52 mg/kg, 45% for 104 mg/kg, $P < 0.05$ by Log Rank test). APX001 at 104 mg/kg was as good as LAmB treatment (21-day survival of LAmB-treated mice [n = 20] =50%). APX001 at 156 mg/kg did not enhance survival vs. placebo. Further, APX001 at 104 mg/kg and LAmB reduced pulmonary and brain fungal burden by ~1 log and 1.5 log vs. placebo, respectively ($P < 0.05$, by Wilcoxon rank-sum). The 52 and the 156 mg/kg APX001 doses also reduced tissue fungal burden vs. placebo mice (0.5–1.0 log).

Conclusion. APX001 protected immunosuppressed mice from *R. delemar* infection with efficacy similar to that of LAmB. Higher doses of APX001 were not protective despite lowering fungal burden. Continued investigation of APX001 as a novel antifungal agent against mucormycosis is warranted.

Disclosures. **K. J. Shaw**, Amplyx Pharmaceuticals Inc.: Employee, Salary; Linnaeus: Consultant, Consulting fee

1522. Fungal Cytological Profiling of *Candida albicans* Exposed to Diverse Antifungal Agents Including the Novel Gwt1 inhibitor APX001A

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Background. Bacterial cytological profiling accelerates drug discovery efforts by determining the mechanism of action (MOA) of newly developed antibacterial agents. Our goal was to adapt this technology to the identification and study of the MOA of antifungal compounds. Here we explore the utility of Fungal Cytological Profiling (FCP) of *C. albicans* in revealing changes in morphology over time using for 6 antifungal agents with unique MOA using fluorescently labeled compounds that specifically stain a variety of subcellular structures including DNA and membranes. Included in the analysis was the novel broad spectrum Gwt1 inhibitor APX001A, the active moiety of the prodrug APX001 which is currently in clinical trials for invasive fungal infections.

Methods. The MICs of 6 antifungals vs. *C. albicans* were determined by CLSI methodology. For FCP, antifungals were added to cultures (1 × 10^5 cells/mL) in RPMI 1640 (buffered with MOPS) at concentrations near MIC: APX001A (0.064 µg/mL); caspofungin (1 µg/mL); fluconazole (2 µg/mL); flucytosine (2 µg/mL); amphotericin B (1 µg/mL) and nikkomycin (3.33 µg/mL) incubated at 35°C with shaking. At 4 hours and 24 hours, treated cultures were stained with various dyes (for 15 minutes), and staining examined under the fluorescence microscope. Dyes included FM 4–64 (membranes), DAPI (DNA), and Sytox Green (cell viability). High-resolution fluorescence microscopy, image analysis and quantitation of cytological parameters (cell length, width, shape, DNA content) were used to create a cytological profile for each growth condition.